

REMARKS

Claims 1, 4-11, 15-21, 56-60 and 63-68 are pending and stand rejected in this application. Applicants respectfully request reconsideration of pending claims 1-11, 15-21, 56-60, and 63-68.

The title of the application has been amended herein to include injectable solutions as presently claimed. No new matter has been added by way of this amendment.

I. Telephonic Interview

The Examiner is thanked for taking the time to speak with Applicants' representatives, Tamera Pertmer and Anthony M. Insogna on November 14, 2006 regarding the Office Action mailed October 30, 2006, as well as the references cited therein.

A. Prior Claim Amendments

Applicants' representatives inquired as to the Examiner's reasons for the current rejections, given that the Examiner had previously indicated in the Final Office Action mailed June 2, 2006 that the claims were allowable if rewritten in independent form. Applicants' representatives reiterated that the claim amendments filed October 2, 2006 were in response to the Examiner's indication that these claims were deemed allowable, and the amendments were for the *sole* purpose of advancing the prosecution of this application to allowance. Applicants' representatives also reminded the Examiner that the claims were amended into the current form by the *Examiner's invitation*. In particular, claims 1 and 11 were amended and new claims 63-68 were added. Claims 1 and 11 were amended to incorporate all the recitations of dependent claims 61 and 62, respectively (cancelled), and new claims 63-68 paralleled the recitations of claims 8-10 and 19-21, respectively.

B. Cited References

Applicants' representatives explained to the Examiner the novelty and unobviousness of the currently pending claims over Bachtsi, either alone or in combination with Tarara, as well as Boschetti, either alone or in combination with Tarara. The specifics of our arguments are provided in greater detail below.

II. Rejection Under 35 U.S.C. § 103

A number of rejections under 35 U.S.C. § 103 have been made by the Examiner. In order to fully address the Examiner concerns, each ground of rejection will be discussed individually below.

A. Bachtsi

Claims 1, 4-6, 11, 15-18 and 56-60 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Bachtsi *et al.* (1995) *J. Microencapsulation*, 12:23-25 ("Bachtsi") (Office Action, part 6).

Applicants respectfully traverse this ground of rejection.

In support of the rejection, the Examiner cites the particle preparation steps disclosed in Bachtsi:

The dehydrated particles were subsequently suspended in a NaOH buffer solution (pH 8-9) overnight to remove any unreacted chemicals. The crosslinked particles were then washed several times with distilled water until the pH of the washing medium reached a value of 7... Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Bachtsi *et al.* and generate sterile microspheres crosslinked PVA [*sic*]... wherein the aldehydes on the microspheres are neutralized because Bachtsi *et al.* disclose crosslinked PVA microspheres that meet the limitations of the instant invention... The neutralized aldehydes attached to the microspheres are obvious because based on the procedure of generating the microspheres of the prior art, Bachtsi *et al.* disclose

that the particles were suspended in NaOH buffer and washed several times with distilled water such that a neutral pH was obtained. As a result, a skilled practitioner in the art would recognize that NaOH acts as a neutralizing agent.

(Office Action, page 4, emphasis in text). The Examiner then refers to a dictionary definition of sodium hydroxide, which indicates NaOH can be used as a neutralizing agent in petroleum refining.

Respectfully, the Examiner may be misunderstanding the rationale for using the NaOH in Bachtisi. Bachtisi states that the NaOH buffer solution (pH 8-9) is used to “remove any unreacted chemicals” (Bachtisi, page 25). For example, skilled artisans will appreciate that organic acids are a byproduct of the glutaraldehyde crosslinking reaction (see Bachtisi, page 25), requiring washing and (pH) neutralization in later steps. In addition, acetic acid and sulfuric acid are also used in the formation of the particles (*Id.*). That is, the NaOH buffer was added as a high pH wash solution to eliminate and/or pH neutralize any acids or other “chemical junk” leftover from the prior, highly acidic reaction steps. Distilled water was then used as a secondary wash solution to reduce the pH to 7 (a neutral pH), after being at a basic pH 8-9. That is, NaOH and distilled water were used to wash the beads and obtain a neutral pH, and not to neutralize aldehydes on microspheres as presently claimed. In support of this idea that NaOH is used as a wash and pH buffer, the Examiner attention is further directed to, *e.g.*, page 27 of Bachtisi, in which NaOH is used to adjust the pH of a solution to 8.0.

The Examiner has provided no evidence to indicate that the reaction steps described in the Bachtisi reference are such that would result in presently claimed microspheres, or that reaction of a simple NaOH wash buffer with unreacted aldehydes would react as required to neutralize aldehydes as presently claimed. (Applicants maintain that there is none). Bachtisi only uses sulphuric acid, PVA and glutaraldehyde, unlike the reactants used in the instant case.

In particular, and in contrast to Bachtisi, the present specification exemplifies chemical reaction conditions that neutralize aldehydes as presently claimed. For instance, the Examples in the specification use a “Tris-HCl” buffer. As those skilled in the art will appreciate, “Tris” is tris(hydroxymethyl)-aminomethane, a well known organic molecule having a primary amino group, which reacts unambiguously with aldehyde groups that are still present on the surface of the beads. In addition to Tris, other amino alcohols having a primary amino group disclosed in the specification are 2-aminoethanol, aminosorbitol and glucosamine (see, originally filed claim 30).

In view of the above, Applicants submit that the present claims are non-obvious over the disclosure of Bachtisi. Accordingly, reconsideration and withdrawal of this ground of rejection is respectfully requested.

B. Tarara

The Examiner has rejected claims 1, 4, 5, 8, 11, 15, 17, 19-21, 56-60 and 63-68 under 35 U.S.C. § 103 as allegedly unpatentable over Bachtisi in view of Tarara *et al.* (U.S. Patent No. 6,565,885) (“Tarara”) (Office Action, part 7). Applicants note that only Tarara is discussed in part 6 the Office Action.¹ As such, Tarara will be discussed as a stand-alone reference in this section.

Applicants respectfully traverse this round of rejection.

To establish a *prima facie* case of obviousness based on a combination of the content of various references, there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant.” *In re Dance*, 160 F.3d 1339, 1343 (Fed. Cir. 1998) (emphasis added); *In re Paulsen*, 30 F.3d 1475, 1482 (Fed. Cir. 1994) (“In reviewing the Board’s obviousness conclusions, we have been guided by the well-settled principles that the claimed invention must be considered as a whole, multiple cited prior art references must suggest the desirability of being combined, and the references must

¹ The combination of Bachtisi and Tarara is discussed in parts 8-10 of the Office Action, and will be discussed below in greater detail.

be viewed without the benefit of hindsight afforded by the disclosure”) (emphasis added). It is not sufficient that the prior art *can be* modified to produce the claimed invention: the modification is non-obvious unless the prior art suggests the desirability thereof. *In re Laskowski*, 10 USPQ 2d 1397 (Fed. Cir. 1989). Further, the invention as a whole must be considered when determining obviousness, rather than the obviousness of any substitution of modification. *Hybritech v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986).

In support of the rejection, the Examiner is using impermissible hindsight to “pick and choose” various elements from throughout the extensive specification of Tarara, while using the instant claims a roadmap, instead of appreciating Applicants invention as a whole. That being said, the Examiner has also failed to point to any text in the specification related to sterile, cross-linked PVA microspheres useful in embolization, or suspensions thereof. Indeed, Applicants submit that *nowhere* does Tarara disclose or suggest any sterile and/or cross-linked PVA particles, much less sterile, crosslinked PVA microspheres having the very specific combination of elements as recited in the claims. In addition, Tarara fails to disclose or suggest microspheres, wherein the aldehydes on the microspheres are neutralized.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981 (CCPA 1974) (emphasis added). “All words in a claim must be considered in judging the patentability of that claim against the prior art.” *In re Wilson*, 424 F.2d 1382, 1385 (CCPA 1970) (emphasis added).

Thus, at least independent claims 1, 11, 63, 65, 66 and 68 are non-obvious over Tarara. In addition, dependent claims 4-10, 15-21, 56-60, 64, and 67 are also non-obvious over Tarara (see, *e.g.*, *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988) (If an independent claim is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom is nonobvious).

Moreover, Applicants respectfully submit that Tarara is in a non-analogous field. As the Examiner is aware, “[i]n order to rely on a reference as a basis for rejection of an applicant’s invention, the reference must either be in the field of applicant’s endeavor or, if

not, then be reasonably pertinent to the particular problem with which the inventor was concerned.” *In re Oetiker*, 977 F.2d 1443, 1446 (Fed. Cir. 1992). *See also In re Clay*, 966 F.2d 656, 659 (Fed. Cir. 1992) (“A reference is reasonably pertinent if, even though it may be in a different field from that of the inventor's endeavor, it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem.”). The claims are related to microspheres useful in the embolization of blood vessels; whereas, Tarara is related to spray drying methods for forming powder compositions for nasal or pulmonary administration, as well as non-pharmaceutical uses for industrial products, such as spray paint:

Accordingly, it is an object of the present invention to provide methods and preparations that advantageously allow for the nasal or pulmonary administration of powders having relatively high fine particle fractions. It is a further object of the present invention to provide stabilized preparations suitable for aerosolization and subsequent administration to the pulmonary air passages of a patient in need thereof. It is yet another object of the present invention to provide powders that may be used to provide stabilized dispersions. It is still a further object of the present invention to provide powders exhibiting relatively low cohesive forces that are compatible for use in dry powder inhalers.

(Col. 3, lines 20-34; emphasis added).

By way of contrast [to prior art formulations], the present invention uses methods and compositions that yield powder formulations having extraordinarily low bulk density, thereby reducing the minimal filling weight that is commercially feasible for use in dry powder inhalation devices. That is, most unit dose containers designed for DPIs are filled using fixed volume or gravimetric techniques. Contrary to prior art formulations, the present invention provides powders wherein the active or bioactive agent and the excipients or bulking agents make-up the entire inhaled particle.

(Col. 9, lines 9-12; emphasis added). Tarara further states that:

The present invention offers benefits over prior art preparations for use in application which require aerosolization or atomization. In

such non-pharmaceutical uses the preparations can be in the form of a liquid suspension (such as with a propellant) or as a dry powder. Preferred embodiments comprising perforated microstructures as described herein include, but are not limited to, ink jet printing formulations, powder coating, spray paint, spray pesticides, etc.

(Col. 45, lines 2-10; emphasis added).

Applicants submit that there would be no motivation for the ordinary skilled artisan to look to Tarara with respect to the art of embolization and/or to overcome the deficiencies of Bachtisi, as discussed below.

Thus, in view of the above, Applicants submit that the present claims are non-obvious over the disclosure of Tarara. Accordingly, reconsideration and withdrawal of this ground of rejection is respectfully requested.

C. Bachtisi in view of Tarara

The Examiner has also rejected claims 1, 4-6, 11, 15-18, 56-60 and 63-68 under 35 U.S.C. § 103 as allegedly unpatentable over Bachtisi in view of Tarara (Office Action, part 8).

Applicants respectfully traverse this ground of rejection.

Both Bachtisi and Tarara are discussed in detail above, and the arguments are equally applicable with respect to the combination of references.

1. Claims 1, 4-6, 11, 15-18, 56-60

Applicants maintain that neither Bachtisi or Tarara, either alone or in combination, disclose or suggest microspheres, wherein aldehydes on the microspheres are neutralized, as recited in claims 1, 4-11, 15-21, and 56-60. As such claims 1, 4-6, 11, 15-18, 56-60 are non-obvious over Bachtisi, either alone or in combination with Tarara.

2. Claims 63-68

With respect to claims 63-68, Applicants submit that neither Bachtisi nor Tarara, either alone or in combination, disclose or suggest *any* microspheres that are sterile and comprise cross-linked PVA, *much less* microspheres comprising crosslinked polyvinylalcohol, wherein said microspheres (a) have a diameter ranging from about 10 μm to about 2,000 μm , (b) are substantially spherical, (c) are substantially uniform in size and shape, (d) are sterile and further comprise (e) a marking agent (claims 63-64 and 66-67) or anti-angiogenic agent (claims 65 and 68).

At the outset, Applicants point out that the Examiner has not rejected claims dependent claims 7-10 or 19-21, over the combination of Bachtisi in view of Tarara. As such, the Examiner implicitly acknowledges the non-obviousness of these claims over the cited references. Because claims 63-68 parallel the recitations in claims 8-10 and 19-21, respectively, Applicants respectfully submit that these claims are also non-obvious over the cited references.

As the Examiner is aware, to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981 (CCPA 1974) (emphasis added).

The Examiner acknowledges that Bachtisi fails to disclose or suggest sterile microspheres (Office Action, page 3) or various types of cell adhesion promoters, marking agents, and anti-angiogenic agents (Office Action, page 7). In an attempt to supply the deficiency in the teachings of Bachtisi, the Examiner cites Tarara as teaching cell adhesion promoters, marking agents and anti-angiogenic agents.

However, it would not have been obvious to modify the microspheres of Bachtisi with the marking agents and anti-angiogenic agents disclosed in Tarara to produce the claimed microspheres useful for embolization having the recited properties.

First, one skilled in the art in the field of embolization would not even look at Bachtshi for any teaching with respect to particles for use in embolization. While it is true that Bachtshi discloses in introductory remarks that hydrogels had been used in the past for drug, enzyme and antibody delivery, the reference does not teach or make obvious the claimed microspheres for use in embolization. These statements, at best, are only an invitation to explore hydrogels in the context of drug delivery. The statement gives no guidance whatsoever as to what to what properties the hydrogels should have or in what fields to explore the use of hydrogels. Further, these statements are in no way specific as to the particular form of the instantly claimed microspheres. Applicants also point out that even though active embolization is a form of embolization that delivers drugs, embolization and microencapsulation for drug delivery via the gut as disclosed by Bachtshi are significantly different and independent arts. Thus, one of ordinary skill in the art of embolization would not even look to art in the field of gut drug delivery.

Moreover, the mere fact that “hydrogels” existed in the prior art as enzyme, drug, and antibody delivery systems, does not lead one to conclude that the microspheres of Bachtshi should be modified to be sterile, comprise a marking agent or anti-angiogenic agent, and/or would be useful in the field of embolization.

As those skilled in the art are aware, many drug application forms do not require sterile ingredients. For example, pills, ointments, nasal drops, *etc.*, are kept in a clean environment, but do not necessarily have to be sterilized, and tend to be applied or ingested in a non-sterile environment.

Additionally, the subject matter of Bachtshi is concerned with release properties of enzyme-loaded PVA microspheres. The ultimate purpose for studying the enzyme release properties of the microspheres is unclear from Bachtshi. Nowhere do the authors disclose or suggest that these enzyme-loaded microspheres would be suitable for (1) any pharmaceutical composition, (2) any medical treatment generally, (3) for embolization specifically, and/or (4) any patient population whatsoever, *much less* that the particles should be sterile, comprise a

marking agent or anti-angiogenic agent, and/or would be useful in the field of embolization, as recited in the claims.²

In an attempt to cure the deficiencies of Bachtisi, the Examiner cites Tarara, which discloses spray drying methods for forming powder compositions for nasal or pulmonary administration, as well as non-pharmaceutical uses for industrial products, such as spray paint.

However Tarara does nothing to correct the deficiencies of Bachtisi. As described Bachtisi does not teach or suggest microspheres useful for embolization comprising sterile crosslinked-PVA microspheres that comprise a marking agent or anti-angiogenic agent. Similarly, Tarara does not teach or suggest, and is not enabling for, microspheres useful for embolization comprising sterile crosslinked-PVA microspheres that comprise a marking agent or anti-angiogenic agent. Tarara discloses spray drying methods for forming powder compositions for nasal or pulmonary administration. Tarara does not disclose or suggest that the aerosolized powder formulations (*e.g.*, comprising fluorocarbons) would be effective for embolization, nor would one skill in the art expect this.

Moreover, the requisite motivation to substitute the teachings of Bachtisi with Tarara is completely lacking. "To establish a *prima facie* case of obviousness based on a combination of the content of various references, there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant." *In re Dance*, 160 F.3d 1339, 1343 (Fed. Cir. 1998); *see also In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."); *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992) (modification of the teachings of a prior art reference is not established by the teachings of a second prior art reference "unless the

² Generally speaking, enzymes would not need to be protected by encapsulation if they were to be injected as the microspheres and sterile solutions presently claimed. Indeed, such delivery avoids the harsh conditions of the gut. Thus, although unsaid, microencapsulation by Bachtisi is most clearly for oral delivery of enzymes, and oral compositions are vastly different from the compositions recited in the claim 1.

prior art suggests the desirability of the modification”(emphasis added)). Respectfully, Applicants submit that the Examiner’s use of hindsight-based obviousness analysis is inappropriate to determine the motivation of a skilled artisan at the time the application was filed.

For at least these reasons, Applicants submit that claims 63-68 are non-obvious over Bachtisi. Accordingly, reconsideration and withdrawal of this ground of rejection is respectfully requested.

D. Boschetti in view of Tarara

The Examiner has also rejected claims 1, 4-11, 15-21, 56-60 and 63-68 under 35 U.S.C. § 103 as allegedly unpatentable over Boschetti in view of Tarara (Office Action, parts 9-10).

Applicants respectfully traverse this ground of rejection.

The Examiner cites Boschetti as teaching microspheres useful for embolization comprising hydrophilic acrylic polymers. However, the chemistry of the microspheres of Boschetti is completely different than PVA, and if anything, actually *teach away* from using PVA as the polymers of Boschetti were an alternative to commercially available, irregularly shaped PVA particles (see below).

However, the Examiner correctly acknowledges that Boschetti fails to disclose microspheres comprising a polyvinyl alcohol or microspheres, wherein aldehydes on the microsphere are neutralized.

To supplement the teachings of Boschetti, the Examiner cites Tarara as teaching “that polyvinyl alcohol and acrylic acid polymers are equivalent microsphere structures” but does not provide a citation to such alleged teaching. The Examiner also states that one skilled in the art would be motivated to replace one polymer with another because Tarara discloses that

both polymers may be used in the formation of microsphere structures. The Examiner further contends:

Thus, a skilled practitioner in the art would not expect the overall properties of the microspheres to drastically change by replacing an acrylic polymer with polyvinyl alcohol. In regards to the aldehydes on the microspheres being neutralized, such property would be inherent because the microspheres generated by the prior art and Applicant because since the same microspheres and components thereof are utilized, a skilled practitioner in the art would recognize that a product is inseparable from its properties.

(Office Action, page 11).

"In order to rely on a reference as a basis for rejection of an applicant's invention, the reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned." *In re Oetiker*, 977 F.2d 1443, 1446 (Fed. Cir. 1992).

Tarara is discussed in detail above. For essentially the same reasons, Applicants again submit that the Examiner has provided no evidence whatsoever as to why one skilled in the art would be motivated to combine references in completely unrelated fields. That is the Examiner has provided no rationale as to why one skilled in the art of therapeutic embolization would look to Tarara in the field of aerosolized powder drug delivery mechanisms in the first place. Indeed, there was no motivation or suggestion in the art to do so, and, in fact, the art actually taught away from PVA-based microspheres.

The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re Hedges*, 783 F.2d 1038 (Fed. Cir. 1986) (Applicant's claimed process for sulfonating diphenyl sulfone at a temperature above 127°C was contrary to accepted wisdom because the prior art as a whole suggested using lower temperatures for optimum results as evidenced by charring, decomposition, or reduced yields at higher temperatures.).

Furthermore, "[k]nown disadvantages in old devices which would naturally discourage search for new inventions may be taken into account in determining obviousness." *United States v. Adams*, 383 U.S. 39, 52 (1966).

At the priority date of the present application, *i.e.*, in October 1998, it is correct that materials useful for embolization, *e.g.*, hydrophilic acrylic-based materials were known. *See, e.g.*, Flandroy *et al.* "Clinical Applications of Microspheres in Embolization and Chemoembolization: A Comprehensive Review and Perspectives," (1993) *In: Pharmaceutical Particulate Carriers in Medical Applications*, Vol. 61, edited by Rolland, A. New York: Marcel Dekker, Inc., pp. 321-366 at page 329 ("Flandroy"), a review article provided as reference K04 in the Supplemental IDS filed November 7, 2006, a copy of which is submitted herewith for the Examiner convenience.

However, the majority of particles were made from materials other than PVA, for example, silicone, glass, dextran, polylactide (PLA), poly(2-hydroxyethyl methacrylate) (PHEMA), trisacryl gelatin, and dextran gelatin. *Id.* This was due to the fact that particles composed of other non-PVA material were of greater interest and believed to be easier to obtain compared to PVA particles. However, when it comes to PVA, the standard at the priority date, and for many years prior, was IVALON, a PVA particle of irregular shape (*see, e.g.*, page 2, line 9 – page 3, line 2 and page 7, line 13 – page 8, line 2 of the specification), which were known to have several disadvantages.

With respect to PVA, Flandroy merely mentions, but does not cite any reference to, spherical PVA (Flandroy, page 329). In fact, the most detailed discussion of PVA particles is of the non-spherical, irregularly shaped IVALON particles (*Id.* at page 328). Flandroy states that the IVALON particles "are not degradable and their immobilization is more proximal than expected" and concludes that "[t]hus, the wrong choice of an embolic material can lead to a proximal occlusion that is as ineffective [sic] as a surgical ligature" (*Id.*) (emphasis added).

Several other references are cited in Flandroy with respect to exemplary spherical particles: Ref. 26 discloses dextran microparticles, Ref. 27 discloses dextran, gelatin, trisacryl microparticles (which include the hydrophilic acrylic microspheres of Boschetti), Refs. 28-31 and 33 discloses poly(2-hydroxyethyl methacrylate) (PHEMA) particles, and Ref. 32 discloses poly(methyl methacrylate) (PMMA) particles. Again, certain of these particles were of greater interest to the skilled artisan and, thus, teach away from working with PVA material in an effort to solve any problems known to exist with irregular PVA particles.

Importantly, however, none of these Refs. 26-33 cited in Flandroy discloses a spherical PVA particle, the desirability of such a PVA particle, nor how to obtain such a PVA particle. Indeed, the final paragraph of the section on page 330 of Flandroy concludes that, although there are some potential drawbacks, these exemplary non-PVA spherical particles are “suitable” materials for effective occlusions.

Thus, after reading Flandroy, one skilled in the art would have no need to look further for other polymeric particles for embolization. Indeed, Flandroy actually teaches away from the claimed microspheres by (1) teaching that only non-PVA spherical particles were suitable for embolization, and (2) PVA was the “wrong choice” for embolic material. As such, a skilled artisan reading Flandroy would have been made aware of the “disadvantages in old devices which would naturally discourage search for new inventions” and would not have been motivated to make the claimed PVA microspheres.

Thus, for at least these reasons, Applicants submit the pending claims are non-obvious over Boschetti, either alone or in combination with Tarara. Accordingly, reconsideration and withdrawal of this ground of rejection is respectfully requested.

III. Conclusion

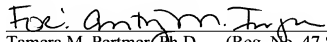
In view of the foregoing amendments and remarks, Applicants respectfully submit that this application is now in condition for immediate allowance. If the Examiner disagrees,

Applicants respectfully request that the Examiner call the undersigned at the number listed below.

A Petition for a Three (3) Month Extension of Time, including provisions for the required fee, is submitted herewith, which extends the response period from January 30, 2007 to, and including, April 30, 2007.

Applicants believe no other fees are due in connection with this response. However, if there are any fees due, please charge them to Deposit Account 50-3013. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above or in the Petition filed concurrently herewith, such an extension is requested and the fee should be charged to our Deposit Account. Also, please charge any fees underpaid or credit any fees overpaid to the same Deposit Account.

Respectfully submitted,



Tamera M. Pertmer Ph.D. (Reg. No. 47,856)

For: Anthony M. Insogna (Reg. No. 35,203)
JONES DAY
222 East 41st Street
New York, NY 10017-6702
(212) 326-3939

Date: April 11, 2007